

PATENT COOPERATION TREATY

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INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference SMC 60613WO	FOR FURTHER ACTION		See Form PCT/PEA/418
International application No. PCT/GB2004/003206	International filing date (day/month/year) 23.07.2004	Priority date (day/month/year) 25.07.2003	
International Patent Classification (IPC) or national classification and IPC C07D207/34, C07D309/10, C07D309/30, C07D405/06			
Applicant AVECIA PHARMACEUTICALS LIMITED et al			
<p>1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36.</p> <p>2. This REPORT consists of a total of 7 sheets, including this cover sheet.</p> <p>3. This report is also accompanied by ANNEXES, comprising:</p> <p style="margin-left: 20px;">a. <input type="checkbox"/> sent to the applicant and to the International Bureau a total of sheets, as follows:</p> <p style="margin-left: 40px;"><input type="checkbox"/> sheets of the description, claims and/or drawings which have been amended and are the basis of this report and/or sheets containing rectifications authorized by this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions).</p> <p style="margin-left: 40px;"><input type="checkbox"/> sheets which supersede earlier sheets, but which this Authority considers contain an amendment that goes beyond the disclosure in the international application as filed, as indicated in Item 4 of Box No. I and the Supplemental Box.</p> <p style="margin-left: 20px;">b. <input type="checkbox"/> (sent to the International Bureau only) a total of (indicate type and number of electronic carrier(s)) , containing a sequence listing and/or tables related thereto, in computer readable form only, as indicated in the Supplemental Box Relating to Sequence Listing (see Section 802 of the Administrative Instructions).</p>			
<p>4. This report contains indications relating to the following items:</p> <p><input checked="" type="checkbox"/> Box No. I Basis of the opinion</p> <p><input type="checkbox"/> Box No. II Priority</p> <p><input type="checkbox"/> Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability</p> <p><input type="checkbox"/> Box No. IV Lack of unity of invention</p> <p><input checked="" type="checkbox"/> Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement</p> <p><input type="checkbox"/> Box No. VI Certain documents cited</p> <p><input type="checkbox"/> Box No. VII Certain defects in the international application</p> <p><input type="checkbox"/> Box No. VIII Certain observations on the international application</p>			
Date of submission of the demand 14.12.2004		Date of completion of this report 30.06.2005	
Name and mailing address of the international preliminary examining authority:  European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465		Authorized Officer Telephone No. +49 89 2399- 8701 	



**INTERNATIONAL PRELIMINARY REPORT
ON PATENTABILITY**

International application No.
PCT/GB2004/003206

Box No. I Basis of the report

1. With regard to the **language**, this report is based on the international application in the language in which it was filed, unless otherwise indicated under this item.
- ☐ This report is based on translations from the original language into the following language, which is the language of a translation furnished for the purposes of:
- ☐ international search (under Rules 12.3 and 23.1(b))
 - ☐ publication of the international application (under Rule 12.4)
 - ☐ international preliminary examination (under Rules 55.2 and/or 55.3)
2. With regard to the **elements*** of the international application, this report is based on *(replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report)*:

Description, Pages

1-12 as originally filed

Claims, Numbers

1-14 as originally filed

- ☐ a sequence listing and/or any related table(s) - see Supplemental Box Relating to Sequence Listing
3. ☐ The amendments have resulted in the cancellation of:
- ☐ the description, pages
 - ☐ the claims, Nos.
 - ☐ the drawings, sheets/figs
 - ☐ the sequence listing (*specify*):
 - ☐ any table(s) related to sequence listing (*specify*):
4. ☐ This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).
- ☐ the description, pages
 - ☐ the claims, Nos.
 - ☐ the drawings, sheets/figs
 - ☐ the sequence listing (*specify*):
 - ☐ any table(s) related to sequence listing (*specify*):
- * If item 4 applies, some or all of these sheets may be marked "superseded."

**INTERNATIONAL PRELIMINARY REPORT
ON PATENTABILITY**

International application No.
PCT/GB2004/003206

Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or Industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes: Claims	1-14
	No: Claims	
Inventive step (IS)	Yes: Claims	1-14
	No: Claims	
Industrial applicability (IA)	Yes: Claims	1-14
	No: Claims	

2. Citations and explanations (Rule 70.7):

see separate sheet

Re Item V.

The following document is referred to in this communication:

D1: WOA-92/06968 (30 April 1992);

D2: WO-A-2004/027075 (*1 April 2004*);

D3: WO-A-2004/096788 (*11 November 2004*);

The current assessment is based on the assumption that all claims enjoy priority rights from the filing date of the priority document(s).

If it later turns out that this is not correct, the documents D2 and D3 as cited in the International Search Report could become relevant.

1. NOVELTY (Article 33(2) PCT):

The present application satisfies the criterion set forth in Article 33(2) PCT because the subject-matter of **claims 1-14** is new in respect of prior art as defined in the regulations (Rule 64(1)-(3) PCT):

The process of the present independent **claim 7** is novel over the process of the prior art D1 on account of the starting material, i.e. the **compound of formula (3)** (cf., the present 2-(2-aminoethyl)-4-hydroxy-6-(oxo- or hydroxy-)-**tetrahydropyran** derivative of the general formula (3) and the *'butyl 6-(2-aminoethyl)-2,2-dimethyl-1,3-dioxane-4-acetate* of the example 4 (Step A) of D1).

The process of the present independent **claim 1** comprises the process of the present claim 7 (cf., the process step c)) and is therefore also novel over D1.

The present independent compound **claim 11** relates to **novel** compounds of formula (3) (see, above) and the present independent process **claim 5** to a process for their preparation.

The present independent compound **claim 8** relates to **novel** precursors of the novel compounds of formula (3) (which also comprise the structural feature which distinguishes the compounds of formula (3) from the prior art (cf., the 4-oxy-2-(oxo- or oxy-)-**tetrahydropyran** ring)) and the present independent process **claim 4** to a process for their preparation.

The present independent compound **claim 14** is directed to certain **novel** compounds of formula (5) which are useful in the preparation of the compounds of formula (7) according to the novel process of the present claim 1.

2. INVENTIVE STEP (Article 33(3) PCT):

The present application also satisfies the criterion set forth in Article 33(3) PCT because the subject-matter of **claims 1-14** appears to involve an inventive step (Rule 65(1)(2) PCT):

Document **D1** - which is considered to represent the **closest prior art** - teaches (cf., the example 4) a process for the preparation of the compound 5-(4-fluorophenyl)-2-(1-methylethyl)-N,4-diphenyl-1-[2-(4-hydroxy-6-oxo-2H-tetrahydro-pyran-2-yl)ethyl]-1H-pyrrole-3-carboxamide which comprises the steps of

- (i) coupling the compound '*butyl* 6-(2-aminoethyl)-2,2-dimethyl-1,3-dioxane-4-acetate with 4-fluoro- α -(2-methyl-1-oxopropyl)- γ -oxo-N, β -diphenyl-benzene-butaneamide (cf., Step A), and
- (ii) deprotecting and hydrolysing the so obtained (4R-cis)-'*butyl* 6-[2[2-(4-fluorophenyl)-5-(1-methylethyl)-3-phenyl-4-[(phenylamino)carbonyl]-1H-pyrrol-1-yl]ethyl]-2,2-dimethyl-1,3-dioxane-4-acetate (cf., Step B).

The process of the present **claim 7** differs from the process of **D1** essentially in that the diketone of formula (4) (cf., the 4-fluoro- α -(2-methyl-1-oxopropyl)- γ -oxo-N, β -diphenyl-benzene-butaneamide of **D1**) is coupled with a 2-(2-aminoethyl)-4-hydroxy-6-(oxo- or hydroxy-)-**tetrahydropyran** derivative (cf., the compound of formula (3)).

In the light of the prior art **D1** the **problem** underlying **claim 7** of the present application resides in the provision of a further process for the preparation of 2-[(2-(pyrrol-1-yl)ethyl]-4-hydroxy-6-oxo-tetrahydropyran derivatives.

This problem has been solved by the process of the present **claim 7** (cf., the present examples 5-9).

As the available prior art does not suggest the use of 2-(2-aminoethyl)-4-hydroxy-6-(*oxo- or hydroxy-*)-**tetrahydropyran** derivatives for the preparation of the 2-[(2-(pyrrol-1-yl)ethyl)-4-hydroxy-6-oxo-tetrahydropyran derivatives of the present formula (5) it is considered that the subject-matter of the present **claim 7** involves an inventive step as set forth in Article 33(3) PCT.

The present independent process **claim 1** comprises the coupling step according to the present claim 7 and is therefore also considered to meet the criteria of Article 33(3) PCT.

The present independent compound **claims 8, 11 and 14** relate to (key) intermediates of the (inventive) process of the present claim 1 (*all* comprising the structural feature which distinguishes the present intermediates from the *2,2-dimethyl-1,3-dioxane-4-acetate* intermediates of the prior art (cf., the *4-oxy-6-(oxo- or oxy-)-tetrahydropyran* ring of the present compounds of formulae (2), (3) and (5))) and are therefore also considered to involve an inventive step.

The present independent process **claims 4 and 5** are directed to the preparation of the (inventive) intermediates of the present claims 8 and 11 and are therefore also considered to involve an inventive step (Article 33(3) PCT).

3. INDUSTRIAL APPLICABILITY (Article 33(4) PCT):

The subject-matter of the present **claims 1-14** concerns chemical processes and chemical compounds and is therefore considered to be industrial applicable in the sense of Article 33(4) PCT.

4. MISCELLANEOUS:

- 4.1. The document D1 should have been cited (Rule 5.1(a)(ii) PCT).
- 4.2. There is an inconsistency in the definition of the substituent group R³ in the present claims 2 (cf., page 14, line 17), 7 (cf., page 17, line 11) and 14 (cf., page 18, line 21): "...R³ represents an *aryl* group, preferably a *4-fluorophenyl* group...". The term "aryl" as used in the art refers to aromatic *hydrocarbon* groups, i.e., not to *substituted* phenyl groups such as a *4-fluorophenyl* group.
- 4.3. The explanations of the terms
 "alkyl" (cf., page 2, line 20: "...the alkyl group may be *cyclic*...",
 "alkenyl" (cf., page 3, line 1: "The alkenyl group may carry *one* or *more*
 substituents...", and
 "aryl" (cf., page 3, line 4: "...which may include cycloalkyl, aryl or *heterocyclic*
 rings..."),
as given in the description (cf. the passages as indicated hereinbefore) do not
harmonize with the usual meaning of these terms as commonly accepted in the
art.
The person skilled in the art would not understand
 (i) the term "alkyl" as also including *cyclic* moieties (the latter would be
 designated as "cycloalkyl" groups rather than "alkyl" groups),
 (ii) the term "alkenyl" (which is used in the art to describe unsaturated alkyl
 groups) as also including *substituted* alkenyl groups,
 (iii) the term "aryl" (which is used in the art to describe aromatic *hydrocarbon*
 groups) as also including *hetero*-fused aryl groups.
This creates an inconsistency between the claims and the description, which
leads to a doubt concerning the extent of protection afforded by the claims, thus
rendering the claims unclear (Article 6 PCT).
- The same observation applies to the passage on page 3, lines 7-14 of the present
description according to which the "hydrocarbonyl groups" R¹ and R³ may be
substituted (the term "hydrocarbonyl" as used in the present claims refers to a
hydrocarbon radical, i.e., not to a *substituted* hydrocarbon radical).
- 4.4. The statement on page 6, line 16 concerning the incorporation of a chemistry text
book is obviously irrelevant and unnecessary in the sense of Rule 9.1(iv) PCT.